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Pesticide Fact Sheet Number 132
Sodium Salt of Fomesafen

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16. Abstract (Limit: 200 words)

This document contains up-to-date chemical information, including a summary of the Agency's regulatory position and rationale, on a specific pesticide or group of pesticides. A Fact Sheet is issued after one of the following actions has occurred.

1. Issuance or reissuance of a registration standard,
2. Issuance of each special review document,
3. Registration of a significantly changed use pattern,
4. Registration of a new chemical, or
5. An immediate need for information to resolve controversial issues relating to a specific chemical or use pattern.

17. Document Analysis a. Descriptors

Pesticides, regulations, Chemical Information Fact Sheet, Use Patterns, Science Findings

b. Identifiers/Open-Ended Terms

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EPA

Pesticide Fact Sheet

Name of Chemical: Sodium Salt of Fomesafen
Reason for Issuance: New Chemical Registration
Date Issued: April 1987
Fact Sheet Number: 132

1. Description of Chemical

Generic Name:	Sodium Salt of 5-[2-Chloro-4-(trifluoromethyl)-phenoxy]-N-(methylsulfonyl)-2-nitrobenzamide
Common Name:	Sodium Salt of Fomesafen
Trade Name:	Reflex, Flex
EPA Shaughnessy Code:	123802
Chemical Abstracts Service (CAS) Number:	72178-02-0
Year of Initial Registration:	1987
Pesticide Type:	Herbicide
Chemical Family:	Diphenyl ethers
U.S. and Foreign Producers:	ICI Americas Inc. New Murphy Road & Concord Pike Wilmington, DE 19897

2. Use Patterns and Formulations:

Application Sites: Fomesafen is proposed for use on soybeans.

Types of formulations: 21.7% Liquid Concentrate End-Use Product

Types and methods of application: End-use product is applied postemergence by ground application. Contact activity results in relative rapid knockdown of weeds in 3 to 5 days. Residual activity may result through root uptake from the soil if rainfall occurs soon after application.

Application rates: The proposed maximum application rate is 0.375 lb/ai/acre with one application per growing season.

Usual carrier: Water

3. Science Findings

Summary Science Statement:

Fomesafen has been found to be oncogenic in mice and has been classified as a Group C oncogen (possible human carcinogen). A quantitative risk estimate has been conducted for the use of fomesafen on soybeans. Based on a $Q^* = 1.9 \times 10^{-1}$ (mg/kg/day) and using a Theoretical Maximum Residue Contribution (TMRC) of 0.0000115 mg/kg (1.5 kg diet) the "worst case" dietary risk was calculated to be 2.2 incidences in a million (2.2×10^{-6}). Using the TMRC provides a conservative estimate since it does not consider the effect of processing on residue levels in the raw agricultural commodity, that actual residue levels will be lower than the level of detection (0.05 ppm), and that less than 100 percent of the crop is treated.

Based on exposure estimates for use of fomesafen on soybeans and the Q^*, the following ranges in risk numbers were calculated:

Private applicators:	
Farmers in South	10^{-5}
Farmers in North Central	10^{-4} to 10^{-5}
Commercial applicators:	
In South	10^{-4}
In North Central	10^{-4}

These estimates assume that workers are wearing long-sleeved shirts, long pants, and shoes; protective gloves are worn during mixing, loading, and application; and 10 percent dermal absorption.

Fomesafen is not considered to be teratogenic and the chemical did not significantly impair reproductive ability in a two-generation reproductive effects study in rats. Four mutagenicity studies with fomesafen were negative. Two rat bone marrow cytogenic tests were positive.

Fomesafen is not acutely toxic to humans, avian species, freshwater fish and invertebrates, honey bees or marine species. The pesticide is slightly toxic to marine invertebrates. A minimum adverse effect is expected on nontarget organisms. Fomesafen is relatively stable to hydrolysis, moderately to very mobile in some soils and may persist at significant levels beyond 1 year; it may contaminate ground water.

An applicator carcinogenic warning, ground water advisory, and crop rotation restrictions are required to appear on the product's labeling.

Chemical Characteristics:

Color: White (PGAI)
Physical State:
Aqueous paste (technical)
Solid (PGAI)
Odor: Faint, sweet
Melting point: 220-221 °C PGAI
Specific gravity: 1.28 PGAI
Solubility:
H_2O - 50 mg/L
Acetone - 300 g/L
Methanol - 25 g/L
Xylene - 1.9 g/L
Hexane - 0.5 g/L
Cyclohexane 150 g/L
Stability: > 6 months at 50 °C

Toxicology Characteristics:

Acute effects[1/]:

Acute oral toxicity (rat):
1,250-2000 mg/kg (males);
1,595-5,203 mg/kg (females);
Toxicity Category III
Acute dermal toxicity: > 780 mg/kg
Primary eye irritation (rabbit): Corneal opacity, iritis and conjunctivitis with remission before 7th day;
Toxicity Category II
Primary skin irritation (rabbit):
Slight erythema graded PIS = 0.58
Toxicity Category III
Dermal Sensitization: Acid form produced dermal sensitization.
Sodium salt produced no sensitization.

Subchronic effects:

Subchronic oral toxicity studies in the rat and the dog show that the liver is the primary target of toxicity in both sexes. Rats were dosed at 1, 5, 100, and 1000 ppm in the diet. The lowest-observed-effect level (LOEL) in this study was 100 ppm (5 mg/kg/day) and the no-observed-effect level (NOEL) was 5 ppm (0.25 mg/kg/day). The dogs were dosed at 0.1, 1, and 25 mg/kg/day. The LOEL in this study was 25 mg/kg/day and the NOEL was 1 mg/kg/day.

A 21-day subchronic dermal toxicity study in the rabbit, at doses of 10, 100, and 1000 mg/kg/day, showed moderate to severe skin irritation at the application site but no

1/ See 40 CFR 162.10 for discussion of toxicity categories and companion labeling requirements.

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systemic effects at doses up to 1000 mg/kg/day. The LOEL for skin irritation was 100 mg/kg/day and the NOEL was 10 mg/kg/day.

Chronic-effects:

Chronic Feeding/Oncogenicity - A 2-year feeding study in Wistar albino SPF rats at doses of 1, 5, 100, and 1000 ppm in the diet also identified the liver as the target organ. The LOEL in this study was 100 ppm based on increased hylinization of liver cells and pigmentation of Kupffer cells at 100 ppm in males, and the NOEL is 5 ppm. No evidence of oncogenicity was reported in this study.

The 2-year feeding study in Charles River CD-1 mice, at doses of 1, 5, 10, 100, and 1000 ppm in the diet, was positive for oncogenic response. A statistically significant increased incidence of liver adenomas were observed in males at 1, 100, and 1,000 ppm and females at 100 and 1000 ppm. A statistically significant increased incidence of liver carcinomas in both sexes was observed at 1000 ppm.

Developmental toxicity:

Rats were dosed with 0, 50, 100, and 200 mg/kg/day fomesafen in the diet and in a second study the same strain of rats at the same laboratory were dosed with 0, 1.0, 7.5, and 50 mg/kg/day fomesafen. In the first study alterations of the 14th rib and increased ossification of the heel bone were observed only at 50 mg/kg/day. These effects were not repeated in the second study. The NOEL is 7.5 mg/kg/day. The maternal LOEL is 200 mg/kg/day with increased post-implantation loss and decreased body weight. No terata were observed under conditions of the studies.

Rabbits were dosed with 0, 2.5, 10, and 40 mg/kg/day fomesafen in the diet. The NOEL is 10 mg/kg/day and there were no adverse effects on offspring under conditions of the study.

Two-Generation reproduction - rat:

Wistar-derived rats (30/sex/dose) were dosed with 0, 50, 250, and 1000 ppm fomesafen in the diet. Significant effects in survival index and litter weight gain at the 1000 ppm were seen. The NOEL for this study is the mid-dose 25 ppm. No meaningful effects were seen at 50 ppm.

Mutagenicity:

Gene-mutation tests in Salmonella and hamster kidney fibroblasts were negative. In vivo chromosomal aberration

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studies in the rat bone marrow were considered positive.

Physiological and biochemical characteristics:

Foliar absorption: Contact activity results in relatively rapid knockdown of weeds in 3 to 5 days.

Translocation: In the presence of rainfall, plants absorb fomesafen from the soil by root uptake.

Environmental characteristics:

Persistence:

Fomesafen is relatively stable to hydrolysis. The half-life was estimated to be about 3 years at 25 °C and does not appear to be pH dependent. In Northern aerobic soils the half-life is approximately 1 year. In Southern anaerobic soils fomesafen's half-life is less than 5 weeks. Laboratory data indicate rapid degradation of parent compound under anaerobic conditions, but degradates were not adequately identified, and where identified, were not monitored in field studies. Therefore, half-lives in Southern anaerobic soils do not provide an accurate estimate of total soil residues.

Absorption and leaching:

Fomesafen aged residues are moderately mobile in loams and clay loams, mobile in sands, and very mobile in coarse sands. The only residue identified was parent. Most of the radiolabeled residues at 20 to 30 cm depth of the coarse sand were unidentified.

Bioaccumulation:

[^{14}C]Fomesafen residues have a low potential for bioaccumulation in bluegill sunfish exposed in a flowthrough system. Maximum bioconcentration factors of < 6X occurred in viscera after 7 and 14 days of exposure to [^{14}C]fomesafen at 1 ppm. Accumulated residues were depurated rapidly; < 50% of the residues in viscera were eliminated after 1 day of depuration.

Crop rotation:

Confined and field rotation studies with wheat are conflicting. Significant uncharacterized residues are present in wheat chaff and straw at about a 1-year rotation interval, but in the field study where only parent was analyzed, no residues were present. Lack of confirmation that parent represents 25 percent of residues in the confined study preclude acceptance of the field data.

Environmental fate and surface and ground water contamination concerns:

Fomesafen may possibly contaminate ground water. Additional data are required before the Agency can fully assess the potential for ground water contamination.

Ecological Characteristics:

Avian acute oral toxicity (Mallard duck):	> 5000 mg/kg
Avian subacute dietary toxicity (Mallard duck and bobwhite quail):	> 20,000 ppm
Freshwater fish acute toxicity -	
Rainbow trout:	680 ppm
Bluegill sunfish:	6030 ppm
Freshwater invertebrate acute toxicity (Daphnia):	330 ppm
Marine fish acute toxicity (Sheepshead minnow):	> 163 ppm
Marine invertebrate acute toxicity -	
Fiddler crab:	> 163 ppm
Pink shrimp:	> 212 ppm
Marine embryolarvae acute toxicity (Pacific oyster):	> 96.6 ppm
Marine invertebrate acute toxicity (Mysid shrimp):	22.1 ppm
Beneficial insects acute oral and contact toxicity (honey bees):	> 50 ug/bee
Avian reproduction -	
Mallard duck:	NOEL = 46 ppm
Bobwhite quail:	NOEL = 50 ppm
Fish early life stage toxicity (Sheepshead minnow):	54-89 ppm
Freshwater invertebrate life-cycle (Daphnia):	Maximum Acceptable Toxic Concentration (MATC) = 50-100 ppm
Marine invertebrate life-cycle (Mysid shrimp):	MATC = 0.69-1.71 ppm

Field chronic effects for soil annelida (earthworm):	NOEL (-1 yr) = 5 kg/ha
Field chronic effects for micro-arthropods (mites, collembola):	NOEL (-2 yr) = 5 kg/ha

These data indicate that fomesafen is essentially nontoxic to avian, freshwater fish, and invertebrate species and bees; and that it is slightly toxic to aquatic invertebrates. Based on the acute and chronic data no significant problems to nontarget organisms are expected from fomesafen's use on soybeans.

4. Benefits

Fomesafen is one of a number of postemergent herbicides recently registered, or for which registration is pending, for soybeans. Projecting use of these herbicides is difficult due to lack of data on distribution of various weeds controlled, comparative efficacy and lack of information on the failure of preemergent herbicides to provide adequate weed control. Based on the reasonable assumption that 30 percent of soybeans will be treated with postemergent herbicides, lower chemical cost, and on estimated market penetration, benefits range from $10 million to $15 million per year.

Registration of fomesafen would also provide another postemergent herbicide which would increase competition resulting in lower prices. These lower prices could result in benefits up to $30 million per year.

If additional weed control were to result in small yield increases or prevent some weeds from becoming problems in the future, further benefits would occur. However, no data exist to justify such a prediction, or quantify it at this time.

5. Tolerance Assessment

Tolerances have been established for residues of the sodium salt of fomesafen in or on the following raw agricultural commodity (40 CFR 180.):

Commodity	Tolerance (ppm)
Soybeans	0.05

There are no international tolerances/residue limits for fomesafen.

There are sufficient residue chemistry data available to support this tolerance, including plant and animal metabolism, storage stability (for both the parent compound and its metabolites), field residue studies, and analytical methods. Cattle and poultry feeding studies

were not submitted. However, under the proposed conditions of use, measurable residues are not expected to be found in the raw agricultural commodities or fractions. These data are therefore not now necessary.

The Acceptable Daily Intake (ADI) and the Maximum Permissible Intake (MPI) are two ways of expressing the amount of a substance that the Agency believes, on the basis of the results of data from animal studies and the application of "safety" or "uncertainty" factors, may safely be ingested by humans without risk of adverse health effects. The ADI is expressed in terms of milligrams (mg) of the substance per kilogram (kg) of body weight per day (mg/kg/day). The MPI, a related figure, is obtained by assuming a human body weight of 60 kg, and is expressed in terms of mg of substance per day (mg/day).

The Agency has calculated an ADI for fomesafen of 0.0025 mg/kg/day, based on a NOEL of 0.25 mg/kg/day in the rat oncogenicity study and a hundredfold safety factor. The MPI for a 60 kg person is 0.15 mg/day. These tolerances have a theoretical maximum residue contribution (TMRC) of 0.0000115 mg/day in a 1.5 kg diet and would utilize 0.46 percent of the ADI.

6. Summary of Major Data Gaps

- Data required:

Guideline Number	Study	Time Generally Allowed for Response to Data Request
Environmental Fate		
161-2	Photodegradation - water	9 months
161-3	Photodegradation - soil	9 months
162-2	Anaerobic soil metabolism	27 months
163-1	Leaching (degradates)	12 months
164-1	Soil field dissipation	27 months
165-1	Rotational crops (confined)	39 months
-	Ground water monitoring	27 months Interim reports due at 6 months and 18 months

Contact Person at EPA:

Richard F. Mountfort
Product Manager (23)
Registration Division (TS-767C)
Environmental Protection Agency
401 M Street SW.
Washington, D.C. 20460
(703) 557-1830

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